October 31, 2013

Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Cerebral artery stent
[Brand name]	Wingspan Stent System
[Applicant]	Stryker Japan K.K.
[Date of application]	September 14, 2012 (Application for marketing approval)

[Results of deliberation]
In the meeting held on October 31, 2013, the Committee on Medical Devices and *In-vitro* Diagnostics made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved with a re-examination period of 3 years under the following conditions for approval. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Take appropriate measures in cooperation with related academic societies to ensure that the product will be used by physicians with sufficient knowledge and experience in the treatment of intracranial arterial stenosis at medical institutions with an established system for handling possible complications associated with the treatment.

2. Take appropriate measures in cooperation with related academic societies to ensure that the product will be used, in compliance with the indication, by physicians (specified in 1 described above) who have acquired the skills for handling the product for endovascular treatment and sufficient knowledge of possible complications associated with the treatment by attending relevant training courses or by other means.

3. Perform use-results surveys of all patients treated with the product until data from a specific number of patients have been accumulated; report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency; and take appropriate measures as necessary.

Review Report

October 8, 2013
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Cerebral artery stent
[Brand name]	Wingspan Stent System
[Applicant]	Stryker Japan K.K.
[Date of application]	September 14, 2012
[Items warranting special mention]	Priority Review
[Reviewing office]	Office of Medical Devices I

Review Results

October 8, 2013

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Cerebral artery stent
[Brand name]	Wingspan Stent System
[Applicant]	Stryker Japan K.K.
[Date of application]	September 14, 2012

[Results of the review]
Wingspan Stent System (Wingspan stent) is a stent system consisting of a self-expanding nitinol stent and a delivery system designed to maintain the lumen patency of the cerebral vessel through implantation at the stenotic site of an intracranial artery.

As nonclinical evaluation data, the following data were submitted: data on stability and durability, data on performance including physicochemical properties and biological safety, and data on the manufacturing process. The data did not show any particular problems.

As clinical evaluation data, results of a Japanese clinical study in patients with transient ischemic attack (TIA) or cerebral stroke that was refractory to medical therapy and caused by ≥50% stenosis of an intracranial artery that was accessible to the product were submitted. The Wingspan stent was implanted in 19 of 20 patients who underwent the procedure. Ipsilateral stroke or death, the primary endpoint, occurred in 2 of the 19 patients (10.5%). Technical success, a secondary endpoint, was achieved in 16 of 19 patients (84.2%) and procedural success, another secondary endpoint, was achieved in 14 of 19 patients (73.7%). Adverse events for which a causal relationship to the Wingspan stent or the procedure could not be ruled out occurred in 12 of 20 patients (60%). All adverse events were those commonly observed in intracranial endovascular treatment of cerebrovascular diseases. Nine serious adverse events occurred in 6 patients (30.0%); major events were 3 events of cerebral infarction in 3 patients (15.0%) and 1 event each of TIA, cerebral haemorrhage, stroke, and vascular perforation in 1 patient each (5.0%). The study results suggest that Wingspan stent may be a treatment option for patients who do not respond to medical therapy. However, it is reported that in the SAMMPRIS Trial which was conducted after the market launch in the US to directly compare “aggressive medical management alone” and “a combination of aggressive medical management and the Wingspan stent,” the rate of stroke in the target vascular region or death within 30 days after treatment was higher in patients who had undergone “a combination of aggressive medical management and the Wingspan stent” compared with those who had undergone “aggressive medical management alone,” although the patient population studied was different from that enrolled in the Japanese clinical study. Taking account of these findings, the indication of the Wingspan stent was investigated.

In Japan, intracranial arterial stenosis is treated with percutaneous transluminal angioplasty using a balloon angioplasty catheter. However, when angioplasty has caused vessel dissection, acute occlusion, or impending occlusion, or when the angioplasty has been found insufficiently effective, there is no approved medical device indicated for such cases in Japan, and a coronary stent is used off-label instead. Taking account of these situations, it is considered that the use of the Wingspan stent for the treatment of vascular dissection, acute occlusion, and impending

occlusion is clinically acceptable, based on the results of the Japanese clinical study which demonstrated that the product was able to reach and be implanted at the lesion site in the treatment of vascular dissection, acute occlusion, or impending occlusion. In light of the results of the SAMMPRIS Trial, the Wingspan stent should not be used in preference to aggressive medical management at present. However, the Wingspan stent does not have any efficacy or safety problem precluding the treatment of patients who show no response to aggressive medical management and in whom angioplasty has been found insufficiently effective or has caused vascular dissection or impending occlusion.

Based on the above, the Pharmaceuticals and Medical Devices Agency concluded that the Wingspan stent should be indicated as follows.
The Wingspan stent is used in percutaneous transluminal angioplasty for intracranial arterial stenosis using a balloon angioplasty catheter in either of the following conditions:

- Emergency treatment of vascular dissection, acute occlusion, or impending occlusion caused during angioplasty
- Re-treatment of patients after angioplasty when there is no other effective treatment option

Since appropriate use of the Wingspan stent is critical in order to ensure the efficacy and safety of the Wingspan stent, guidelines etc., should be established on the appropriateness of intracranial endovascular treatment of cerebral arterial stenosis, in cooperation with related academic societies. In addition, the following conditions for approval should be imposed: (i) appropriate measures should be taken to ensure that physicians with sufficient knowledge and experience use the product in compliance with the treatment guidelines established by related academic societies, and (ii) the product should be used in medical institutions with an established system for handling adverse events associated with intracranial endovascular treatment of cerebrovascular diseases in order to prevent the aggravation of complications caused by percutaneous angioplasty of intracranial cerebral arteries.

The Wingspan stent was implanted at the stenotic site of an intracranial artery in only 19 patients in the Japanese clinical study, and the product was used for emergency treatment in only 2 patients. Therefore, in the post-marketing surveillance, information should be collected from all patients treated with the product until data from a specific number of patients have been accumulated in order to confirm the safety and efficacy, and that this should be included in the conditions for approval.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the Wingspan stent may be approved for the following intended use with the following conditions for approval, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
The Wingspan stent is used in percutaneous transluminal angioplasty for intracranial arterial stenosis using a balloon angioplasty catheter in either of the following conditions:

- Emergency treatment of vascular dissection, acute occlusion, or impending occlusion caused during angioplasty
- Re-treatment of patients after angioplasty when there is no other effective treatment option

[Conditions for approval]
The applicant is required to:

1. Take appropriate measures in cooperation with related academic societies to ensure that the Wingspan stent will be used by physicians with sufficient knowledge and experience in the

treatment of intracranial arterial stenosis at medical institutions with an established system for handling complications associated with the treatment.

2. Take appropriate measures in cooperation with related academic societies to ensure that the Wingspan stent will be used, in compliance with the indication, by physicians (specified in 1 described above) who have acquired the skills for handling the product for endovascular treatment and sufficient knowledge of possible complications associated with the treatment by attending relevant training courses or by other means.

3. Perform use-results surveys of all patients treated with the Wingspan stent until data from a specific number of patients have been accumulated; report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency; and take appropriate measures as necessary.

Review Report

October 8, 2013

I. Product for Review

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Cerebral artery stent
[Brand name]	Wingspan Stent System
[Applicant]	Stryker Japan K.K.
[Date of application]	September 14, 2012
[Proposed intended use]	The Wingspan stent is intended to be used to maintain the patency of a blood vessel through implantation at the stenotic site within an intracranial blood vessel in patients with transient ischemic attack or cerebral stroke that is refractory to medical therapy and caused by ≥50% stenosis of the cerebral artery that is accessible to the product.

II. Product Overview

The Wingspan stent is a stent system consisting of a self-expanding revascularization device (stent, Figure 1) designed to maintain the patency of a blood vessel through implantation at the stenotic site within an intracranial artery, together with a delivery system (Figures 2 and 3). The delivery system consists of a delivery catheter (outer body, inner body) and a rotating hemostasis valve. The stent is pre-loaded within the lumen of the distal end of the delivery catheter (outer body).

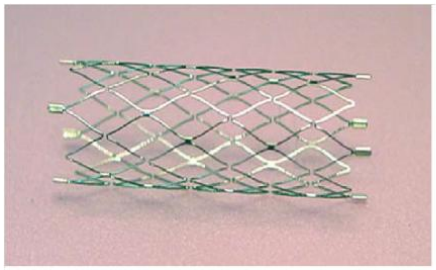

Figure 1. Stent

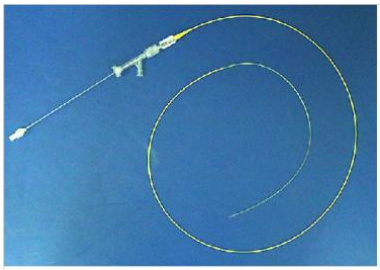

Figure 2. Delivery system

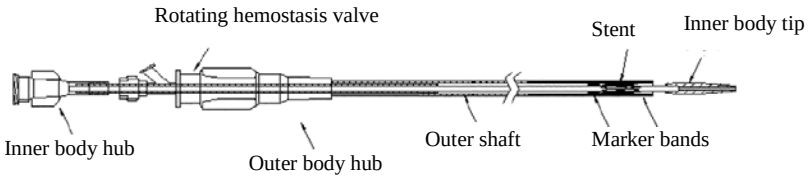

Figure 3. Overview

The stent is a nickel-titanium alloy (nitinol) tubular mesh, with platinum-iridium alloy marker bands attached at both ends for improved visibility. In order to allow appropriate selection according to the diameter of the target blood vessel and the length of stenosis, the stent is available in 5 different outer diameters (2.5, 3.0, 3.5, 4.0, 4.5 mm) and 3 different lengths (9, 15, 20 mm), with 15 types in total. Retracting the outer body of the catheter at the lesion site causes self-expansion of the stent, resulting in deployment.

III. Summary of the Submitted Data and the Outline of the Review by Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors of the Expert Discussion on the Wingspan stent declared that they do not fall under Item 5 of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Origin or history of discovery

Cerebral infarction is the third leading cause of death in North America, Europe, and Asia.[1] In Japan also, with the westernization of lifestyle and aging of the population, occlusive cerebrovascular disorder accounts for an increasing percentage of cerebrovascular disorders. In particular, there is a conspicuous increase in the incidence of intracranial atherosclerosis that occurs against the background of lifestyle diseases such as diabetes mellitus, hypertension, and dyslipidemia.[2,3,4]

Symptomatic intracranial atherosclerotic arterial stenosis is first treated with medical therapy using warfarin or aspirin (anticoagulant therapy, antiplatelet therapy). However, a study conducted to compare warfarin and aspirin in patients with intracranial atherosclerotic arterial stenosis (WASID Study) showed that 25% of patients with 70%-90% stenosis experience cerebral infarction within 2 years in the ipsilateral side regardless of whether they were treated with either warfarin or aspirin, suggesting the limit of medical therapy in severe symptomatic intracranial arterial stenosis.[5]

Another treatment option for intracranial atherosclerotic arterial stenosis is bypass surgery. However, the main target of this surgical procedure is complete occlusion, and it is unclear to what extent the procedure is effective in patients with stenosis. Also, it is reported that in a study comparing extra-intracranial bypass surgery and medical therapy in patients with middle cerebral artery stenosis, cerebral stroke within 30 days occurred more frequently in patients who underwent the surgery.[6] It is also reported that residual sequelae and death after surgery occurred at a higher rate in patients who received posterior circulation bypass surgery.[7,8] Thus, bypass surgery-associated complications occur at a relatively high rate.

Against this background, attempts of percutaneous translumina1 angioplasty (PTA) for intracranial atherosclerotic arterial stenosis began in 1980s as a treatment method that may allow recovery of anterograde blood flow, aided by the technical progress in endovascular treatment. In Japan, a balloon angioplasty catheter "BSC balloon catheter for dilating cerebral blood vessels (OTW) (approval number, 21300BZY00535000; foreign brand name, Gateway™ PTA Balloon Catheter)" was approved for intracranial endovascular treatment in October 2001 and is now used in clinical practice. In order to treat vascular dissection, acute occlusion, or impending occlusion which occurs at a certain rate during PTA and to improve the rate of long-term patency by preventing restenosis, the concurrent use of a coronary artery stent started and the effectiveness of the method began to be reported.[9,10] However, since the coronary artery stent is expanded by inflating the balloon and is designed for use in coronary arteries which are morphologically different from cerebral arteries, serious complications such as vascular injury and acute/subacute vascular occlusion arising from its use in cerebral arteries have been reported.[11,12]

Against this backdrop, the Wingspan stent was developed as a self-expanding nitinol stent with the purpose of maintaining the patency of the blood vessel through implantation at the stenotic site of an intracranial artery.

The Wingspan stent is approved under humanitarian device exemption (HDE) in the US, based on the evaluation that it may be a novel therapeutic strategy in patients with symptomatic stenosis in major intracranial arteries that poorly responds to medical therapy. Taking account of this situation, the product was designated as a device that requires early introduction at "The Ninth Meeting of Study Group on the Early Introduction of Medical Devices etc., with High Medical Need" held in October 2008 and based on the results of the discussion at the meeting, the product was designated as a priority review item on October 25, 2012 by the Ministry of Health, Labour and Welfare (MHLW).

1.(2) Usage conditions in foreign countries

The Wingspan stent was approved under HDE by the US Food and Drug Administration (FDA) on August 3, 2005 with the purpose of maintaining the patency of the blood vessel through its implantation at the stenotic site of the intracranial blood vessel in patients with transient ischemic attack (TIA) or cerebral stroke that is refractory to medical therapy and caused by ≥50% stenosis of the intracranial stenotic lesion. In Europe, the product was granted CE marking on December 6, 2005. A total of [redacted] units were sold in major foreign countries during the period from February 2009 through June 2013.

The indication of the product in the US was modified as follows according to the instructions issued on August 2012 by the FDA based on the results of the SAMMPRIS Trial to be discussed later [see "8. Clinical Data"]. Simultaneously with the modification of the indication in the US, the indication in Europe was also modified to the same one as that in the US.

[Modified indication in the US]

The product is used for the treatment of an intracranial artery in patients who are aged ≥22 and ≤80 years, have had 2 or more cerebral strokes, are receiving aggressive medical management, and have 70%-99% atherosclerotic intracranial arterial stenosis that are accessible to the system. Before treatment with the product, at least 7 days must have passed since the onset of the most recent symptomatic stroke. Treatment with the product is most appropriate for patients with modified Rankin Scale of ≤3.

1.(3) Occurrence of events associated with the product

The incidence of events reported during the survey period from February 2009 through June 2013 was as follows: death, 0.22% ([redacted] events); serious malfunction, 0.59% ([redacted] events); and device malfunction, 0.16% ([redacted] events). Reported main adverse events and malfunctions were as follows: restenosis, 0.16% ([redacted] events); thrombosis, 0.14% ([redacted] events); stent placement failure, 0.07% ([redacted] events); vascular dissection, 0.03% ([redacted] events); insufficient stent expansion , 0.03% ([redacted] events); stent breakage, 0.01% ([redacted] events); catheter breakage, 0.01% ([redacted] events); and vessel perforation, catheter disconnection/disengagement/breakup/contamination, 0.01% ([redacted] events).

2. Setting of specifications

2.A Summary of the submitted data

Specifications of performance or functions at the submission include shortening rate, radial pressure, corrosion resistance, and durability of the stent; tensile strength of the outer body of the delivery catheter, tensile strength of the inner body of the delivery catheter; coating durability and radiopacity of, and microparticles on the delivery system. Also, safety-related parameters include biological safety, sterility, residue on ethylene oxide gas sterilization, and bacterial endotoxin.

2.B Outline of the review by PMDA

As a result of reviewing the specifications, including "5. Performance" to be described later, in regard to the appropriateness of the attributes tested and acceptance criteria, PMDA accepted the proposed specifications.

3. Stability and durability

3.A Summary of the submitted data

Stability data were omitted from submission based on the justification that stability was validated by in-house real time stability testing of ≥3 years. Instead, the applicant's declaration was submitted which stated that the shelf life was determined based on the necessary stability evaluation according to "Handling of stability studies related to the determination of the shelf life in the Applications for Approvals (Certifications) for Marketing Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

3.B Outline of the review by PMDA

PMDA accepted the applicant's view that the shelf life of the Wingspan stent should be 3 years.

4. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act

A declaration of conformity declaring that the Wingspan stent meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act (hereinafter referred to as "Essential Principles") (MHLW Ministerial Announcement No.122, 2005) was submitted.

PMDA reviewed the product's conformity to the Essential Principles and accepted the declaration.

5. Performance

5.(1) Studies supporting safety

5.(1).1) Physicochemical tests

5.(1).1).A Summary of the submitted data

In order to detail the physicochemical properties of the stent, data of the following tests were submitted: validation of the durability of the implant under pulsating load and bending load by finite element analysis (FEA), free area, length of the implanted stent, shortening rate, outer diameter of the implanted stent, adhesion of marker bands, radial pressure, recoil and shape recovery temperature, MRI conformity, corrosion velocity test, fatigue test, and surface characterization. All data demonstrated the conformance of the Wingspan stent to the specifications.

In order to detail the physicochemical properties of the delivery system, data of the following tests were submitted: coating particles, delivery system-derived microparticles during stent placement, tensile strength of the outer body (hub attachment site, proximal/central part of shaft, distal/central part of shaft), tensile strength of the inner body (proximal part of hub/shaft, hub/hypotube, proximal/distal part of shaft, marker band at the distal part of the shaft, distal tip), lubricity of the coating, appearance (system, rotating hemostasis valve, dual tapered tip, gap between tips, connections at the proximal and distal part of the outer body), coating length of the outer body, length of the proximal part of the inner body, length from the distal end of the stent to the tip of the outer body, outer diameter at the distal tip of the inner body, readiness of the system (should be ready for flushing), conformity of 6F guide catheter, advance of the system, guidewire-following capability, stent placement, inner diameter of the shaft of the inner body, inner diameter at the proximal end of the shaft of the outer body, inner diameter at the distal end of the shaft of the outer body, effective length of the delivery system, variable length of the outer body, length of the distal part of the shaft of the inner body, outer diameter of the marker band at the distal end of the shaft of the outer body, outer diameter at the central part of the shaft of the outer body, outer diameter at the proximal end of the shaft of the outer body, outer diameter of the marker band at the distal end of the shaft of the inner body, outer diameter at the central part of the shaft of the inner body, outer diameter at the distal end of the hypotube of the inner body,

adhesion of hypotube, inspection of hub taper (outer body, inner body), and hub air aspiration test (outer body, inner body). All data demonstrated the conformity of the product to the specifications.

5.(1).1).B Outline of the review by PMDA

PMDA asked the applicant to explain the clinical risk caused by overlapped placement of the Wingspan stent and by the placement of the product at the bending part of the blood vessel, and to explain how these risks were evaluated in nonclinical studies.

The applicant responded as follows:
Although overlapped placement may cause stent breakage due to pulsating blood flow, no stent breakage has been reported with use of the Wingspan stent. As for fatigue durability of overlapped stents, it was confirmed that none of the stents broke in a fatigue test in which a total of 48 stents (3.5 mm × 20 mm) were overlapped in pairs and subjected to 400 million cycles of vibrations (frequency, [redacted] Hz). In regards to corrosion of overlapped stents, fretting corrosion, crevice corrosion, and pitting corrosion were observed in 22 of 24 overlapped stent pairs, but no stent fracture was observed, demonstrating sufficient corrosion resistance for ensuring performance. Based on the above results, the applicant considered that the 10-year durability of the overlapped stents was demonstrated and that the product had no durability problem.

Placement of the stent at a bending part of the blood vessel may result in defective placement such as poor adherence to the vascular wall, causing stent thrombosis and possibly leading to death. There has so far been only 1 case of death due to defective placement of the Wingspan stent in post-marketing reports. In order to evaluate the fatigue durability of the stent implanted at a bending part of the blood vessel, a total of 24 stents (4.5 mm × 20 mm) were implanted at bends and subjected to 400 million cycles of vibration (frequency, [redacted] Hz). Corrosion of the strut was observed in 1 stent, but the radial pressure was within the acceptance criteria. No corrosion was observed after [redacted] cycles of vibration which corresponds to 30 days of placement in actual use, during which blood vessel intima is assumed to have covered the stent completely, from which the applicant considered that the product would have no clinically significant problem. Furthermore, a kink resistance test was performed on the products of 2.5 mm × 20 mm and 4.5 mm × 20 mm in size using a blood vessel model with a curvature radius of [redacted] mm. The results demonstrated the kink resistance of the product.

Based on the above results, the applicant considered that the Wingspan stent was ensured to be effective and safe when implanted in overlap or at a bending part. In order to decrease the residual risk, the Precaution section of the package insert will include the description to the effect that “the selection of the product of an appropriate size is important and the target site of treatment should be fully assessed by angiography before the interventional procedure.

PMDA accepted the applicant’s view.

Based on the above, PMDA concluded that there is no particular problem with the submitted data on the physicochemical properties of the Wingspan stent.

5.(1).2) Biological safety

5.(1).2).A Summary of the submitted data

Biological safety was evaluated based on the “Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market Medical Devices” (PFSB/ELD/OMDE Notification No. 0301-20, dated March 1, 2012) and on ISO 10993 series.

The Wingspan stent (stent, delivery catheter, rotating hemostasis valve) underwent the following tests: cytotoxicity testing, sensitization testing, intradermal testing, as well as testing for acute

systemic toxicity, pyrogenicity, and hemolysis. No toxic reaction was observed in any of the tests. Genotoxicity studies (bacterial reverse mutation study, mouse lymphoma study) of the stent in the product were omitted because the evaluation has already been performed for the stent of Neuroform Stent (approval number, 22400BZX00371000) which is manufactured by the same process using the same raw materials as used for the product. Implantation safety was evaluated with the data from a "180-day basilar artery placement study in dogs" which was conducted to support the manner in which the device is used. In this study, general symptoms, hematology, and clinical chemistry were examined in addition to the evaluation of the local implanted site. No systemic toxic changes were observed. Therefore, no subacute toxicity test was conducted.

The chronic toxicity study and carcinogenicity study were omitted because the applicant considered that there was no particular concern about such risks, based on the results of the acute systemic toxicity study, implantation study, and genotoxicity study.

5.(1).2).B Outline of the review by PMDA

PMDA concluded that there is no particular problem after reviewing the data related to biological safety.

5.(2) Studies supporting the performance of the device

5.(2).A Summary of the submitted data

In order to detail the performance of the delivery system, data on studies on the integrity of the delivery system after stent recross and after stent placement were submitted. All data demonstrated the conformance of the Wingspan stent to specifications.

5.(2).B Outline of the review by PMDA

PMDA reviewed and accepted the data supporting the performance.

5.(3) Studies supporting the usage method of the device

5.(3).A Summary of the submitted data

In order to support the usage method of the Wingspan stent, a 180-day basilar artery placement study in dogs was conducted and the results were submitted.

The Wingspan stent was implanted in the basilar artery of 28 healthy mongrel dogs to evaluate the vascular reactivity in this study. After placement for 30, 90, and 180 days, complications and neurological symptoms were evaluated and after the last angiography, animals were necropsied and subjected to histological evaluation. Abnormalities occurred in 3 of 28 animals. During the placement procedure, stent dislocation occurred in 1 animal and intracranial haemorrhage occurred in 2 animals due to perforation of the target blood vessel by the wire. They died or were euthanized on Day 0. No device-related death occurred at 30, 90, or 180 days after placement, and all animals were considered to be healthy. No neurological symptoms were observed at the timing of euthanasia after the last angiography, and histological examination showed no gross abnormality caused by stent placement, demonstrating that the product has no problem with vascular reactivity.

5.(3).B Outline of the review by PMDA

Three of 28 animals died or were euthanized because of stent dislocation or intracranial haemorrhage caused by perforation of blood vessel by the guidewire. PMDA asked the applicant to justify their determination that these risks are clinically acceptable.

The applicant responded as follows:
This study was conducted to evaluate the reactivity of the blood vessels to the implanted stent. Since it was practically impossible to deliver the stent to the basilar artery of dogs using the

delivery system of the Wingspan stent, a different system was used to deliver and implant the stent. The stent dislocation appeared to have occurred during the placement procedure because the delivery system used was not optimized for implanting the stent of the product.

As for placement performance of the Wingspan stent, it was confirmed in an *in vitro* stent placement study that the stent could be implanted accurately at the intended site. Therefore, using the delivery system of the product, it is possible to implant the stent accurately without dislocation. In the Japanese clinical study using the product, the procedural success rate was 84.2% (16 of 19 patients). In the remaining 3 patients, the procedure was rated as failure because the stenotic rate was not improved to <50% after stent placement. However, the product was implanted appropriately at the intended site in all patients including these 3 patients, from which it was concluded that there is no problem in clinical use.

Vessel perforation caused by the guidewire is common to all endovascular treatments using guidewires and not specific to the Wingspan stent. The risk in clinical use is within the acceptable range when the procedures are performed in consideration of the precautions provided in the package insert of the guidewire used in combination, as is the case with medical devices used for other endovascular treatments.

PMDA accepted the applicant's view.

Based on the above, PMDA concluded that there is no particular problem with the data submitted to support the usage method of the Wingspan stent.

6. Risk analysis

Documents summarizing the risk management system and its implementation status in reference to ISO 14971 "Medical devices - Application of risk management to medical devices" were attached.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process

To provide information on the manufacturing process, data on the manufacturing process, manufacturing facilities, sterilization method (ethylene oxide gas sterilization), and quality control were submitted.

PMDA reviewed and accepted the data on the manufacturing process.

8. Clinical data

Data of the investigator-initiated Japanese clinical study were submitted as evaluation data. Also, data of the Wingspan and Gateway Safety Study,[13] which were submitted for application as evaluation data for HDE approval in the US, were submitted.

In addition, a summary of the discussion of the efficacy and safety of the Wingspan stent, based on the literature review focused on the following studies, was submitted: (i) "NIH registry study in patients with symptomatic intracranial arterial stenosis (stenotic rate ≥70%)"[14] supported by the National Institutes of Health (NIH) in the US; (ii) "Randomized study comparing stenting versus aggressive medical management for intracranial arterial stenosis (SAMMPRIS Trial)"[15] also supported by the US NIH; and (iii) US Wingspan registry study[16] conducted by the US company after market launch.

The main study results are described below.

8.A Summary of submitted data

8.A.(1) Japanese clinical study (investigator-initiated study; study period, [redacted] to [redacted])

A Japanese single-arm clinical study was conducted at 2 centers to evaluate the safety and performance of the device under routine clinical use in patients with TIA or cerebral stroke that was refractory to medical therapy and caused by ≥50% stenosis of an intracranial blood vessel that was accessible to the Wingspan stent.

The main inclusion criterion was patients aged ≥20 and ≤80 years who met all of the following conditions:

(a) Patients had ischemic cerebrovascular disorder[1] that was refractory to medical therapy and was caused by intracranial arterial stenosis.
(b) Modified Rankin Scale of ≤3
(c) The vessel diameter at the target lesion was 2.0 to 4.5 mm as measured by angiography performed at the medical institution where the stent was to be implanted to the patient.
(d) The target lesion was the cause of TIA or cerebral infarction and was in an intracranial artery (internal carotid artery, middle cerebral artery, vertebral artery, or basilar artery) with ≥50% and <100% stenosis as measured by angiography performed at the medical institution.
(e) The length of the target lesion was ≤14 mm as measured by angiography performed at the medical institution.

The following patients were excluded: (i) patients with angiographic findings of vascular intimal injury or dissection at the target lesion that precludes pre-dilation, (ii) patients with a severely calcified lesion or a lesion that prevents access of the Wingspan stent or appropriate dilation, (iii) patients with severe tandem stenoses within an intracranial artery that preclude 1 stent to cover, (iv) patients with intracranial arterial stenosis secondary to vasospasm, basilar meningitis, moyamoya disease, vasculitis, or vascular dissection that was not related to cerebral atherosclerosis.

All of the 20 patients enrolled in the study were included in the safety analysis set. The procedure was discontinued in 1 patient because the internal carotid artery was perforated during the operation of the guidewire to ensure the diameter was appropriate at the placement site. The Wingspan stent was implanted in 19 patients, excluding this patient. A total of 19 patients implanted with the product were included in the full analysis set (FAS) and in the primary analysis set for the primary and secondary endpoints (except adverse events and malfunctions).

The following events/parameters were set as the primary endpoint and the secondary endpoints.

Primary endpoint: occurrence of ipsilateral stroke or death within 6 months after the procedure (only death for which a causal relationship to the product could not be ruled out was to be counted)

Secondary endpoints:

(a) Technical success (stenotic rate improved to <50% immediately after the procedure)
(b) Procedural success (successful stent placement without stroke or death within 3 days)
(c) Restenosis of the target lesion within 6 months after the procedure (≥50% stenosis)
(d) Re-dilation of restenosis of the target lesion within 6 months after the procedure

[1] Conditions wherein neurological symptoms are clinically suspected to be due to ischemia in the vascular area with a stenotic lesion and the suspicion is consistent with the imaging findings (an ischemic lesion is confirmed in the vascular area distal to the stenotic lesion, or no other vascular area has an ischemic lesion causing neurological signs)

(e) Occurrence of TIA or stroke in subjects who had restenosis of the target lesion within 6 months after the procedure
(f) Ipsilateral stroke or death within 30 days after the procedure
(g) All-cause stroke or death within 6 months after the procedure
(h) Neurological evaluation (modified Rankin Scale, Barthel lndex evaluated before the procedure and at 30 days and 6 months after the procedure; NIH Stroke Scale evaluated before the procedure and at 3 days and 30 days after the procedure)
(i) Adverse events and malfunctions

Table 1 shows the main background characteristics of subjects and lesions in the study. The primary disease was TIA in 10 subjects (50.0%) and cerebral infarction in 10 subjects (50.0%). The lesion site was the left internal carotid artery (at the cranial base) in 6 subjects (30.0%) accounting for the highest proportion, followed by the left middle cerebral artery in 4 subjects (20.0%).

Table 1. Background characteristics of subjects and lesions

Age (years) (mean ± standard deviation [SD])		67.7 ± 6.1
Sex (n [%])	Male	14 (70.0)
	Female	6 (30.0)
Primary disease (n [%])	TIA	10 (50.0)
	Cerebral infarction	10 (50.0)
Modified Rankin Scale before the procedure (n [%])	Grade 0-3	20 (100.0)
	Grade 4-6	0 (0.0)
Lesion site (n [%])	Left internal carotid artery (cranial base)	6 (30.0)
	Right internal carotid artery (cranial base)	2 (10.0)
	Left internal carotid artery (supraclinoid)	0 (0.0)
	Right internal carotid artery (supraclinoid)	0 (0.0)
	Left middle cerebral artery	4 (20.0)
	Right middle cerebral artery	2 (10.0)
	Left vertebral artery	3 (15.0)
	Right vertebral artery	1 (5.0)
	Basilar artery	2 (10.0)
Length of target lesion (mm)		11.21 ± 3.75
Stenotic rate (%) (mean ± SD)		67.9 ± 11.4

Tables 2 and 3 show the analysis results of the primary endpoint and the secondary efficacy endpoints.

The incidence of ipsilateral stroke or death within 6 months after the procedure, the primary endpoint, was 10.5% (2 of 19 subjects), meeting the attainment criterion (44.4%) that had been set based on the rate of stroke or TIA (65.5%, 95% confidence interval [CI] 45.7%-81.6%) in patients with intracranial arterial stenosis refractory to medical therapy. [2] Also, the observed rate was lower than the level (11.1% [2 of 18 subjects]) pre-estimated based on the percentage (7.1%) of “ipsilateral stroke or death within 6 months after the procedure” in the results of the foreign clinical study, the “Wingspan and Gateway Safety Study” [see “8.A.(2) Wingspan and Gateway Safety Study”]. The stenotic rate was 67.9% ± 11.4% (mean ± SD) before the procedure, 34.8% ± 12.7% immediately after the procedure, and 46.1% ± 21.2% at 6 months after the procedure.

Table 2. Results of efficacy endpoints (except neurological evaluation)

	Number of patients (incidence)	95% CI*
Ipsilateral stroke or death within 6 months after the procedure	2/19 (10.5%)	1.3%-33.1%
Technical success	16/19 (84.2%)	60.4%-96.6%
Procedural success	14/19 (73.7%)	48.8%-90.9%
Restenosis of the target lesion within 6 months after the procedure[1]	5/16 (31.3%)	11.0%-58.7%
Re-dilation of restenosis of the target lesion within 6 months after the procedure[1]	0/16 (0.0%)	0.0%-20.6%
Occurrence of TIA or stroke in subjects who had restenosis of the target lesion within 6 months after the procedure[2]	0/5 (0.0%)	0.0%-52.2%
Ipsilateral stroke or death within 30 days after the procedure	2/19 (10.5%)	1.3%-33.1%
All-cause stroke or death within 6 months after the procedure	4/19 (21.1%)	6.1%-45.6%

*: Clopper-Pearson method
1: Evaluated in 16 patients with technical success
2: Evaluated in 5 patients who, among 16 subjects with technical success, had restenosis of the target lesion within 6 months after the procedure

Table 3. Results of efficacy endpoints (neurological evaluation)

	N = 19	N = 19	N = 19
	Before the procedure	30 days after the procedure	6 months after the procedure
Modified Rankin Scale, n (%)			
0	5 (26.3)	6 (31.6)	6 (31.6)
1	6 (31.6)	5 (26.3)	6 (31.6)
2	6 (31.6)	6 (31.6)	6 (31.6)
3	2 (10.5)	2 (10.5)	1 (5.3)
Change in modified Rankin Scale, n (%)			
Aggravated	-	2 (10.5)	2 (10.5)
Unchanged or improved	-	17 (89.5)	17 (89.5)
Barthel Index			
Mean ± SD	98.2 ± 3.8	98.4 ± 3.4	98.7 ± 3.3
Change in Barthel Index, n (%)			
Aggravated	-	0 (0.0)	0 (0.0)
Unchanged or improved	-	19 (100.0)	19 (100.0)
	Before the procedure	3 days after the procedure	30 days after the procedure
NIH Stroke Scale			
Mean ± SD	0.8 ± 1.3	1.0 ± 1.5	0.7 ± 0.9
Change in NIH Stroke Scale, n (%)			
Aggravated	-	2 (10.5)	1 (5.3)
Unchanged or improved	-	17 (89.5)	18 (94.7)

As for safety, adverse events were observed in 19 of 20 subjects (95.0%) who underwent the procedure. Adverse events for which a causal relationship to the Wingspan stent or the procedure could not be ruled out, according to the time of occurrence, were observed in a total of 12 subjects (60%), as shown in Table 4. Diabetes insipidus that occurred after study discontinuation in 1 subject who was not implanted with the product is not included in Table 4. All of the adverse events were those commonly observed in intracranial endovascular treatment.

Nine serious adverse events were observed in 6 subjects (30.0%), consisting of 3 events of cerebral infarction in 3 subjects (15.0%) and 1 event each of TIA, cerebral haemorrhage, stroke, vessel perforation, hydrocephalus, and diabetes insipidus in 1 subject each (5.0%). One subject died in this study. In this subject, the internal carotid artery was perforated (vessel perforation) during the operation of the guidewire to ensure the diameter of the stent placement site was appropriate, which resulted in a cerebrovascular accident (stroke), leading to study discontinuation. The vessel perforation and stroke were treated, but acute hydrocephalus was

confirmed by subsequent CT and diabetes insipidus developed at [redacted] days after study discontinuation, and the subject died [redacted] days after study discontinuation.

One event of vascular occlusion occurred in 1 of 20 subjects (5.0%) in the safety analysis set. This event was detected by cranial MRA which was performed when cerebral infarction occurred at 14 days after the procedure at a site different from the site where the Wingspan stent was implanted. This event did not cause any symptoms, requiring no particular treatment.

Table 4. Adverse events for which a causal relationship to the Wingspan stent or the procedure could not be ruled out according to the time of occurrence

	Interval between commencement of the procedure and use of the product (n = 20)		Use of the product to 30 days after the procedure (n = 19)		30 days to 6 months after the procedure (n = 19)		Total (n = 20)	
System Organ Class (SOC) Preferred term (PT)	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Total incidence	4 (20.0)	6	11 (57.9)	14	1 (5.3)	1	12 (60.0)	21
Vascular disorders	3 (15.0)	3	0 (0.0)	0	0 (0.0)	0	3 (15.0)	3
Vascular dissection	2 (10.0)	2	0 (0.0)	0	0 (0.0)	0	2 (10.0)	2
Vessel perforation	1 (5.0)	1	0 (0.0)	0	0 (0.0)	0	1 (5.0)	1
Ear and labyrinth disorders	0 (0.0)	0	0 (0.0)	0	1 (5.3)	1	1 (5.3)	1
Deafness transitory	0 (0.0)	0	0 (0.0)	0	1 (5.3)	1	1 (5.3)	1
Nervous system disorders	1 (5.0)	2	7 (36.8)	9	0 (0.0)	0	8 (40.0)	11
Subarachnoid haemorrhage	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.0)	1
TIA	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.0)	1
Hydrocephalus	1 (5.0)	1	0 (0.0)	0	0 (0.0)	0	1 (5.0)	1
Headache	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.0)	1
Cerebrovascular accident	1 (5.0)	1	0 (0.0)	0	0 (0.0)	0	1 (5.0)	1
Cerebral infarction	0 (0.0)	0	3 (15.8)	3	0 (0.0)	0	3 (15.8)	3
Cerebral haemorrhage	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.0)	1
Vagus nerve disorder	0 (0.0)	0	2 (10.5)	2	0 (0.0)	0	2 (10.5)	2
Skin and subcutaneous tissue disorders	0 (0.0)	0	2 (10.5)	2	0 (0.0)	0	2 (10.5)	2
Haemorrhage subcutaneous	0 (0.0)	0	2 (10.5)	2	0 (0.0)	0	2 (10.5)	2
General disorders and administration site conditions	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.3)	1
Puncture site induration	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.3)	1
Gastrointestinal disorders	1 (5.0)	1	0 (0.0)	0	0 (0.0)	0	1 (5.3)	1
Vomiting	1 (5.0)	1	0 (0.0)	0	0 (0.0)	0	1 (5.3)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.3)	1
Hiccups	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.3)	1
Investigations	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.3)	1
Blood pressure decreased	0 (0.0)	0	1 (5.3)	1	0 (0.0)	0	1 (5.3)	1

8.A.(2) Wingspan and Gateway Safety Study[13] (study period, [redacted] to [redacted] 20[redacted])

A multi-center, uncontrolled, open-label study was conducted in 12 centers in Europe and Asia to evaluate the safety and performance of the Wingspan stent in patients who had recurrent stroke caused by intracranial atheromatous disease that was refractory to medical therapies, and had ≥50% stenosis of an intracranial blood vessel that is accessible to the product.

The main inclusion criterion was patients aged ≥18 and ≤80 years who met all of the following conditions.

(a) Recurrent stroke caused by the target lesion that was refractory to medical therapy
(b) Modified Rankin Scale of ≤3
(c) No new neurological symptoms within 24 hours before enrollment

(d) At least 7 days have passed since the stroke occurred before enrollment
(e) Diameter of the target blood vessel was 2.5 to 4.5 mm.
(f) Stenosis of the blood vessel at the target lesion was ≥50% as measured by DSA or MRA performed within past 6 months.
(g) The length of the blood vessel at the target site was ≤14 mm.

The following patients were excluded from the study: (i) patients who showed clinical symptoms of acute cerebral ischemia and in whom acute and subacute ischemic signs were observed on CT at the vascular area of the target site, (ii) patients with angiographic findings of vascular intimal injury or dissection at the target lesion precluding pre-dilation, (iii) patients with a severely calcified lesion or a lesion that prevents access of the Wingspan stent or appropriate dilation, (iv) patients with other lesions that could cause stroke, such as cardiogenic embolism or severe proximal tandem stenoses of the extracranial vertebral artery or carotid artery.

The primary safety endpoint was death or ipsilateral stroke assessed by neurological examination at 30-day follow-up. The primary efficacy endpoints were as follows: stenting success (the stenotic rate at the target lesion improved to <50% after stent placement); and procedural success (stent placement remained successful without cerebral infarction or death at hospital discharge). The secondary endpoints were as follows: parent vessel dissection evaluated based on the angiogram of the target blood vessel immediately after the procedure and at 6 months after the procedure; incidence of ≥50% symptomatic stenosis or stent migration based on the angiogram of the target blood vessel at 6 months after the procedure; clinical outcome based on the neurological examination at 6 months after the procedure (ipsilateral stroke and death); incidence of stroke at 6 months after the procedure; and access site complications requiring treatment.

One of the 45 patients enrolled in the study died of cerebral haemorrhage 10 days after the procedure, and the remaining 44 patients (97.8%) were treated with the Wingspan stent and were followed up until Day 30 after the procedure. Of these, 42 patients were followed up with clinical and neurological examination up to 6 months after the procedure, and 40 patients were followed up with angiography at 6 months after the procedure. Table 5 shows the main characteristics of the patients and the lesion. The primary disease was TIA in 3 patients (6.7%) and cerebral infarction in 42 patients (93.3%). The lesion site was the vertebral artery in 13 patients (28.9%) accounting for the highest proportion, followed by middle cerebral artery in 10 patients (22.2%).

Table 5. Main characteristics of subjects and lesions

Age (years) (mean ± SD)		66 ± 8
Sex (n [%])	Male	33 (73.3)
	Female	12 (26.7)
Primary disease (n [%])	TIA	3 (6.7)
	Cerebral infarction	42 (93.3)
Modified Rankin Scale before the procedure (n [%])	Grade 0-3	44 (97.8)
	Grade 4-6	1 (2.2)
Lesion site (n [%])	Internal carotid artery (petrous)	5 (11.1)
	Internal carotid artery (cavernous)	4 (8.9)
	Internal carotid artery (bifurcation of ophthalmic artery)	1 (2.2)
	Posterior communicating artery	1 (2.2)
	Internal carotid artery (supraclinoid)	1 (2.2)
	Internal carotid artery (bifurcation area)	1 (2.2)
	Middle cerebral artery	10 (22.2)
	Vertebral artery	13 (28.9)
	Basilar artery	9 (20.0)
Length of target lesion (mm) (mean ± SD)		7.2 ± 2.9
Stenotic rate (%) (mean ± SD)		74.9 ± 9.8

Ipsilateral stroke or death at 30 days after the procedure, the primary safety endpoint, occurred in 2 subjects. One subject experienced ipsilateral haemorrhagic stroke at 24 hours after the procedure and died after 10 days. The clinical event assessment committee concluded that the event was probably causally related to the procedure but a causal relationship to the stent was unclear. Another subject underwent successful treatment and was discharged without any neurological problems but experienced thromboembolic stroke in the deep pons 7 days after the procedure. The clinical event assessment committee concluded that the event was not causally related to the procedure, but a causal relationship to the stent placement was unclear.

Table 6 shows the achievement of the primary efficacy endpoints "stenting success" and "procedural success" and of the secondary efficacy endpoints "incidence of ≥50% restenosis at 6 months after the procedure" and "incidence of stroke or death at 6 months after the procedure." Procedural success was not attained in the 1 fatal case described above; the procedure was regarded as a failure in this case. The stenotic rate was 74.9% ± 9.8% (mean ± SD) before the procedure, 31.9% ± 13.6% immediately after the procedure, and 28.0% ± 23.2% at 6 months after the procedure. At 6 months after the procedure, 3 subjects showed ≥50% stenosis, which were 81%, 60%, and 68%, and were all asymptomatic.

The other endpoints "parent vessel dissection immediately after stent placement or after 6 months" and "stent migration" did not occur. There were 7 reported events of "access site complications immediately after stent placement or after 6 months" (6 events of haematoma, 1 event of abscess) in 5 subjects. Treatment was required for 4 of 7 events.

Table 6. Primary efficacy endpoints and incidence of restenosis, stroke, or death at 6 months after the procedure

	Number of subjects	%
Stenting success	44/44	100
Procedural success	43/44	97.7
≥50% stenosis at 6 months after the procedure	3/40	7.5
Death or ipsilateral stroke at 6 months after the procedure (composite endpoint)	3/42	7.1
Ipsilateral stroke	3/42	7.1
Death	1/42	2.4
All-cause stroke at 6 months after the procedure	4/42	9.5

Within 6 months after the procedure, 26 serious adverse events occurred in 18 of 45 subjects (40.0%), of which 8 events were considered to be related to the device or the procedure, while 18 events were not. Those considered to be related to the device or the procedure were 2 events each of TIA and stroke and 1 event each of cerebral haemorrhage, infection, haematoma at the perforation site, and a new distal in-stent stenosis (Table 7).

Table 7. Serious adverse events that occurred within 6 months after the procedure

	N = 45		Causal relationship with the device or procedure	
	Number of subjects	%	Yes	No
TIA	5	11.1	2	3
Stroke	5	11.1	2	3
Haemorrhagic event	3	6.7	1	2
Acute myocardial infarction	2	4.4	0	2
Infections	2	4.4	1	1
Peripheral vascular disease	2	4.4	0	2
Haematoma	2	4.4	1	1
Fractured metatarsal	1	2.2	0	1
New distal in-stent stenosis	1	2.2	1	0
Pulmonary oedema	1	2.2	0	1
Respiratory failure (epiglottic oedema)	1	2.2	0	1
Syncope	1	2.2	0	1

8.A.(3) SAMMPRIS Trial[15]

This was an NIH-supported multi-center, randomized, comparative study in patients who had ≥70% stenosis in a major intracranial artery and experienced TIA or cerebral infarction within the preceding 30 days. The study compared the following 2 treatment results: (i) aggressive medical management; and (ii) percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan stent in combination with aggressive medical management. Initially, the enrollment of 382 subjects in each group (764 subjects in total) had been planned, but it was found that the incidences of stroke and death during the perioperative period were significantly higher in the PTAS plus aggressive medical management group (PTAS-plus group) compared with the aggressive medical management alone group, as discussed later. Therefore, subject enrolment was terminated when 451 subjects (227 subjects in the aggressive medical management alone group, 224 subjects in the PTAS-plus group) were enrolled.

The main inclusion criterion was patients aged ≥30 and ≤80 years who met all of the following conditions:

(a) Patients who experienced, within 30 days before enrollment, TIA or non-serious cerebral infarction caused by intracranial stenotic lesion with 70%-99% stenosis
(b) Modified Rankin Scale of ≤3
(c) The diameter of the target blood vessel was 2.0 to 4.5 mm.
(d) The length of the blood vessel at the target site was ≤14 mm.

Table 8 shows the main characteristics of the subjects and lesions in each group. In both groups, the middle cerebral artery was the most common lesion site (105 subjects [46.3%] in the aggressive medical management alone group, 92 subjects [41.1%] in the PTAS-plus group), followed by the basilar artery (51 subjects [22.5%], 49 subjects [21.9%], respectively). There was no significant difference between the 2 groups in the characteristics of subjects or lesions, including the mean stenotic rate of the lesion before the procedure.

Table 8. Main characteristics of subjects and lesions

		Aggressive medical management alone group (n = 227)	PTAS-plus group (n = 224)
Age (years) (mean ± SD)		59.5 ± 11.8	61.0 ± 10.7
Sex (n [%])	Male	145 (63.9)	127 (56.7)
	Female	82 (36.1)	97 (43.3)
Primary disease (n [%])	TIA	75 (33.0)	82 (36.6)
	Cerebral infarction	152 (67.0)	142 (63.4)
Lesion site (n [%])	Internal carotid artery	49 (21.6)	45 (20.1)
	Middle cerebral artery	105 (46.3)	92 (41.1)
	Vertebral artery	22 (9.7)	38 (17.0)
	Basilar artery	51 (22.5)	49 (21.9)
Stenotic rate (%) (mean ± SD)		81 ± 7	80 ± 7

Patients in the aggressive medical management group received aspirin 325 mg and clopidogrel 75 mg orally for 90 days after group assignment, and their blood pressure (systolic blood pressure ≤140 mmHg [≤130 mmHg in patients with diabetes mellitus]), lipid level (LDL-C ≤70 mg/dL), and daily habit (smoking abstinence, weight control, exercise therapy) were strictly controlled. Patients in the PTAS-plus group underwent PTAS within 3 days after enrolment in addition to the same treatment that was given in the aggressive medical management group. Patients who did not take clopidogrel 75 mg for at least 5 days before treatment were loaded with 600 mg of clopidogrel at 6 to 24 hours before PTAS.

The primary endpoints were “stroke or death within 30 days after enrolment or within 30 days after the procedure for reperfusion of the target blood vessel” and “cerebral infarction occurring in the target vascular region after ≥30 days.” The secondary endpoints were “all-cause stroke or death,” “fatal stroke,” “myocardial infarction,” “haemorrhagic complications not associated with stroke,” and “all-cause haemorrhagic complications.”

Table 9 shows the results of the 451 patients enrolled in the study (227 patients in the aggressive medical management group, 224 patients in the PTAS-plus group). The incidence of “stroke in the target vascular region or death within 30 days” was 5.8% in the aggressvie medical management group and 14.7% in the PTAS-plus group (P = 0.002, log-rank test). The incidence of “stroke in the target vascular region or death within 1 year” was 12.2% in the aggressive medical management group and 20.0% in the PTAS-plus group (P = 0.009).

Table 9. Results of the primary and secondary endpoints

	Aggressive medical management group (n = 227)	PTAS-plus group (n = 224)	*P* value*
Stroke or death within 30 days	5.8%	14.7%	0.002
Cerebral infarction occcurring in the target vascular region after ≥30 days	5.7%	5.8%	—
Stroke or death within 1 year	12.2%	20.0%	0.009
All-cause stroke or death	17.5%	23.4%	0.06
All-cause stroke	14.9%	22.3%	0.03
Death	4.1%	3.4%	0.95
Fatal stroke	6.4%	9.0%	0.21
Myocardial infarction	4.0%	2.2%	0.60
Haemorrhagic complications not associated with stroke	1.4%	3.6%	0.10
All-cause haemorrhagic complications	1.8%	9.0%	<0.001

* Log-rank test

The above results showed that, in patients who experienced TIA or cerebral infarction due to ≥70% stenosis of a major intracranial artery within 30 days, the risk of cerebral infarction during the early period after PTAS in the PTAS-plus group was higher compared with that in the aggressive medical management alone group, and the risk of cerebral infarction in the aggressive medical management alone group was lower than expected. Based on these results, the applicant considered that the aggressive medical management was superior to PTAS using the product.

8.B Outline of the review by PMDA

PMDA reviewed the data by focusing on the following points.

8.B.(1) Clinical evaluation and indication of the product

8.B.(1).1) Proposed indication and the modified indication in the US

In the US, results of the SAMMPRIS Trial were subjected to subpopulation analysis independently by the FDA and, as a result, the indication criteria were modified in August 2012 as shown in Table 10.

PMDA asked the applicant to explain the reason for using the un-modified US indication in proposing the indication in Japan despite the fact that the US indication of the Wingspan stent was modified in August 2012.

The applicant responded as follows:

The present application is based on the results of the Japanese clinical study that was conducted using the old US indication. There are several differences between the proposed intended use in Japan and the modified US indication. The results of the Japanese clinical study were subjected to stratified analysis regarding these differences. The results did not support the assumption that the differences would cause any disadvantage in patients. Based on the results, the applicant considered that it was appropriate to adopt the old US indication as the intended use of the Wingspan stent in Japan.

Table 10. New and old indications in the US and inclusion criteria in the clinical study

	Original indication in the US	Modified indication in the US	Main inclusion criteria in the Japanese clinical study
Main indication criteria modified in the US			
1	≥20 and ≤80 years old	≥22 and ≤80 years old	≥20 and ≤80 years old
2	Ischemic cardiovascular disorder that is caused by intracranial stenotic lesion and is refractory to medical therapy	Patients who have had 2 or more strokes and are undergoing aggressive medical management	Ischemic cardiovascular disorder that is caused by intracranial stenotic lesion and is refractory to medical therapy
3	50% to <100% stenosis causing transient ischemic attack or cerebral infarction	Recurrent stroke associated with 70%-99% atherosclerotic intracranial arterial stenosis	50% to <100% stenosis causing transient ischemic attack or cerebral infarction
4	—	Modified Rankin Scale of ≤3	Modified Rankin Scale of ≤3
5	—	History of 2 or more strokes, with an interval of 7 days or longer since the most recent one	—
Main exclusion criteria added in the US			
6	—	Treatment within 7 days after onset of the most recent symptomatic stroke	—
7	—	Transient ischemic attack (TIA)	Ischemic cerebrovascular diorder

PMDA considers as follows:

The results of the Japanese clinical study were similar to those in the Wingspan and Gateway Safety Study, and therefore do not exclude the possibility that the Wingspan stent may be a treatment option for patients who do not respond to medical therapy. However, the fact that the

incidence of stroke in the target vascular region or death within 30 days was higher in the group treated with the product in combination with aggressive medical management than in the group receiving aggressive medical management alone in the SAMMPRIS Trial should be taken into due account, although the study population was different from that in the Japanese clinical study. The applicant examined the differences between the modified US indication and the proposed indication in Japan and explained that it is appropriate to adopt the previous US indication as the intended use in Japan because reasons for supposing that the differences would cause disadvantage in patients could not be identified. However, since the Japanese clinical study investigated only 19 subjects, the study population is too small to allow subpopulation analysis of the effect of the differences in the indication between in Japan and in the US. Based on the above, the intended use proposed by the applicant at submission is not acceptable, as judged by the data submitted in the present application.

The US indication was modified based on the subpopulation analysis by the FDA of the results of the NIH-supported SAMMPRIS Trial.[17] As a result, the range of the intended use granted in the initial HDE approval was limited to the range where no significant difference was observed compared with aggressive medical management alone in the SAMMPRIS Trial. Since the applicant did not have raw data of the SAMMPRIS Trial and only submitted the paper of the SAMMPRIS Trial as reference data, it was impossible for PMDA to conduct a detailed review of the SAMMPRIS Trial in the regulatory review. PMDA examined the results of the subpopulation analysis of the SAMMPRIS Trial using the data published on modification of the indication in the US. The examination revealed that only a few dozens of subjects in each group were included in the comparison of parameters with allegedly no significant difference. Also, the US indication was changed from "50% to <100% stenotic lesion" to "≥70% atherosclerotic intracranial arterial stenosis," but the usefulness of the product in target patients was not established using the results of the SAMMPRIS Trial in patients with 70%-99% stenosis in the intracranial blood vessel or those of other submitted studies. Therefore, it is difficult at present to identify the target population in which the benefit of the product outweighs the risk and determine whether the modified US indication is acceptable in Japan.

8.B.(1).2) Clinical significance of the product in Japan

In Japan, a balloon angioplasty catheter for cerebral angioplasty "BSC balloon catheter for expanding cerebral blood vessel (OTW) (approval number, 21300BZY00535000)" was approved in October 2001 and is used clinical practice. PTA using a balloon catheter has drawbacks such as vascular dissection, elastic recoil, and restenosis. In Japan, when cerebral angioplasty using the balloon catheter has been found insufficiently effective or when complications such as vascular dissection have occurred, coronary stents are used off-label because there are no approved alternative medical devices available.

Connors et al. reported that vascular dissection occurred in 14% of 70 patients who underwent PTA for symptomatic intracranial arterial stenosis that was judged to be the lesion responsible for symptoms by the neurologist and the neurosurgeon, that thrombolytic treatment was required in 4% of patients, and that stent backup is essential in PTA for an arteriosclerotic lesion in an intracranial artery.[18] A fact-finding survey was also conducted in Japan, and the results were published as "Study for the preparation of guidelines to ensure the safety of catheter intervention and to educate physicians in charge" (Research Grant for Cardiovascular Diseases, 17C-1 from MHLW).[19] According to this survey, 454 of the 11,281 enrolled patients underwent treatment for intracranial arterial stenosis, and 34% of them required off-label use of the coronary arterial stent, including emergency treatment. Within 30 days after the procedure, 52 patients experienced complications, which included haemorrhagic complications (11 patients), ischemic complications (28 patients), and death (4 patients).

Currently no medical devices have been approved in Japan to be used when vascular dissection or acute occlusion has occurred during PTA using a balloon catheter for treating intracranial arterial stenosis, or when cerebral angioplasty has been found insufficiently effective, and coronary stents are used off-label instead in these occasions. Taking account of such situations, PMDA concluded that there is a high clinical need for the development of a stent for the treatment of intracranial blood vessels.

8.B.(1).3) Usefulness of the product and indication in Japan

In the Japanese clinical study, the technical success rate (stenotic rate improved to <50% immediately after the procedure) was 84.2% (16 of 19 subjects) and the procedural success rate (stenotic rate improved to <50% immediately after stent placement, with no stroke or death occurring within 3 days after the procedure) was 73.7% (14 of 19 subjects). In the Japanese clinical study, there were only 2 patients who had balloon catheter-induced vascular dissection and underwent treatment with the Wingspan stent, and neither ipsilateral stroke nor death occurred in these patients within 6 months after the procedure. In the Wingspan and Gateway Safety Study which did not include cases of vascular dissection, acute occlusion, or impending occlusion, the stenting success rate was 100% (44 of 44 subjects) and the technical success rate was 97.7% (43 of 44 subjects). The above results have shown that the delivery system can reach the target lesion and the stent can be deployed there, from which PMDA concluded that it is clinically acceptable to use the product for treatment of vascular dissection, acute occlusion, or impending occlusion.

The SAMMPRIS Trial failed to demonstrate the clinical significance of using the product in combination with aggressive medical management. However, there are patients who do not respond to aggressive medical management, and if cerebral infarction recurs in such patients, the only treatments available are angioplasty using a balloon catheter and bypass surgery. However, it is reported that angioplasty with a balloon catheter is often accompanied by elastic recoil or restenosis, and bypass surgery is difficult to perform and does not provide favorable results depending on the site of the lesion. In such cases, there are no treatment options other than stent placement. In the SAMMPRIS Trial, the incidence of “stroke in the target vascular region or death within 1 year” was 12.2% in the aggressive medical management group, whereas the rate was 20.0% in the PTAS-plus group. The indicence of “ipsilateral stroke or death within 6 months after the procedure” was 10.5% in the Japanese clinical study and 7.1% in the Wingspan and Gateway Safety Study. Taking account of these findings, PMDA considers that there are no efficacy- or safety-related problems that contraindicate the use of the Wingspan stent in the re-treatment after angioplasty in patients who do not respond to aggressive medical management and for whom no other effective treatment option is available although the treatment using the product should not be conducted in preference to aggressive medical management.

Based on the above, PMDA concluded that the indication of the Wingspan stent in Japan should be as follows.

The Wingspan stent is used in percutaneous transluminal angioplasty for intracranial arterial stenosis using a balloon angioplasty catheter in either of the following conditions:

- Emergency treatment of vascular dissection, acute occlusion, or impending occlusion caused during angioplasty
- Re-treatment of patients after angioplasty when there is no other effective treatment option

8.B.(2) Proper use of the product

PMDA concluded that guidelines, etc., should be established on the appropriateness of intracranial endovascular treatment of cerebral arterial stenosis, in cooperation with related academic societies since proper use is critical to ensure the efficacy and safety of the Wingspan becasuse of the following reasons: the product should not be used if there are any other effective

treatment methods available; it should be taken into account that the product may be used in a certain percentage of the patients when PTA is performed.

PMDA also concluded that the following conditions for the approval should be imposed: (i) appropriate measures should be taken to ensure that physicians with sufficient knowledge and experience use the Wingspan stent in compliance with the treatment guidelines established by the related academic societies, and (ii) the product should be used in medical institutions with an established system for handling possible adverse events associated with intracranial endovascular treatment of cerebrovascular diseases in order to prevent the aggravation of complications caused by percutaneous angioplasty of an intracranial artery.

8.B.(3) Antiplatelet therapy

Antiplatelet therapy is considered to be necessary for a certain period to prevent thrombotic occlusion after the placement of the Wingspan stent. However, at present, there is no adequate evidence for using antiplatelet therapy after stent placement in a cerebral artery. The applicant recommends antiplatelet therapy, as was recommended in the Japanese clinical study, since no particular problems were observed in the study. However, since there were only 19 patients in the Japanese clinical study, PMDA concluded that there is no sufficient evidence to support such a recommendation, and asked the the applicant to explain the drugs used for antiplatelet therapy and the treatment duration in foreign countries.

The applicant responded as follows:

The manufacturer of the Wingspan stent does not recommend any specific antiplatelet therapy in patients treated with the product. However, the Direction for Use of the product provides the following preparation precaution: “Typical antiplatelet and anticoagulation regimen used for interventional intracranial procedures is an important adjunct to Stent treatment. Patients must be advised to take their prescribed medications after the Stent is implanted and should be counseled on the risk of not complying with medical therapy. In-stent thrombosis may occur during the procedure if proper antiplatelet and anticoagulation therapy is not administered.” Also, 2008 joint guidelines of the American Heart Association and the American Stroke Association recommend the following as antiplatelet therapies for patients with stroke or transient ischemic attack, from which it is supposed that similar antiplatelet therapies are performed in patients treated with the Wingspan stent.

(a) Aspirin (50-325 mg/day) monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy.
(b) The combination of aspirin and extended-release dipyridamole is recommended over aspirin alone.
(c) For patients allergic to aspirin, clopidogrel is reasonable.

In Japan, according to Japanese Guidelines for the Management of Stroke 2009, the most effective antiplatelet therapies for preventing the recurrence of noncardiogenic cerebral infarction at present are aspirin (75-150 mg/day) or clopidogrel (75 mg/day) (Grade A), and cilostazol (200 mg/day) or ticlopidine (200 mg/day) (Grade B). Since these dosage regimens are consistent with the following antiplatelet therapies employed in the investigator-initiated Japanese clinical trial of the Wingspan stent, the applicant recommends these antiplatelet therapies after the market launch.

- Before the procedure, 2 or more of the following drugs are administererd: aspirin (81-324 mg/day), clopidogrel (75 mg/day), cilostazol (100-200 mg/day), and ticlopidine (100-200 mg/day).
- After the procedure, the pre-procedural antiplatelet therapy should be continued for at least

4 weeks, after which at least 1 antiplatelet drug should be continued for an indefinite period although the treatment may be changed at the discretion of the physician.

PMDA considers as follows:
At present, there is no evidence for antiplatelet therapy after stent placement in a cerebral artery. However, since it is important to provide information on the dose and treatment period of antiplatelet therapy used in the Japanese clinical study, the Wingspan and Gateway Safety Study, and the SAMMPRIS Trial, the information should be included in the package insert.

8.B.(4) Post-marketing use-results survey

PMDA considers as follows:
The Wingspan stent is an intracranial vascular stent for maintaining the patency of the blood vessel through implantation at the stenotic site in an intracranial artery. It is the first product developed for the above purpose in Japan. In the Japanese clinical study, the Wingspan stent was implanted at the intracranial arterial stenotic site in only 19 patients, and the product was used for emergency treatment in only 2 patients. Therefore, information should be collected from all patients treated with the Wingspan stent via post-marketing surveillance until data from a specific number of patients have been accumulated, and the safety and efficacy of the product should be evaluated, and this should be included in the conditions for approval.

8.B.(5) Results of the Expert Discussion and measures taken

8.B.(5).1) Proposed indication and modified US indication

The following conclusions of PMDA were discussed at the Expert Discussion: (i) consideration should be given to the results of the SAMMPRIS Trial although it was conducted in a patient population different from that in the Japanese clinical study; however (ii) it is difficult at present to identify the target population in whom the benefit of the Wingspan stent outweighs the risk; and (iii) neither the proposed indication nor the modified US indication is acceptable in Japan.

The following comments were raised from expert advisors:
- They agree with the PMDA's conclusion that, taking account of the results of the SAMMPRIS Trial, the indication as used in the Japanese clinical study is not acceptable.
- They also agree with the PMDA's conclusion that the 10.5% incidence of ipsilateral stroke or death observed within 6 months in the Japanese clinical study is hardly a sufficiently satisfactory result and therefore, neither the proposed indication nor the same indication as the modified US indication is acceptable.

On the other hand, the following comments were also raised:
- Greater weight should be placed on the results of the Japanese clinical study.
- Since the results of the FDA's analysis of the SAMMPRIS Trial are understandable, the same indication as the modified US indication may be acceptable.
- The proposed indication may be acceptable provided that the target patients are limited to those refractory to medical therapy and that the patients are clearly informed of the treatment-associated risks.

PMDA considers that the results of the Japanese clinical study are important because they reflect the actual clinical conditions, but the results of the SAMMPRIS Trial should also be taken into due account. The subpopulation analysis of the SAMMPRIS Trial showed no significant difference in some parameters, the analysis of which was performed using data obtained from a limited number of patients, with the usefulness of the Wingspan stent in pertinent patient subpopulations still unclear. Therefore, PMDA explained that evidence of the usefulness of the product is insufficient to allow the indication of the product to include these patient subpopulations.

Upon provision of the above explanations by PMDA, the PMDA's conclusions were finally supported by all the expert advisors.

8.B.(5).2) Indication of the product

During the treatment of intracranial arterial stenosis with a balloon catheter for cerebral angioplasty, vascular dissection, elastic recoil, or restenosis may occur in a certain percentage of patients, and coronay stents are used off-label at present in Japan. Therefore, PMDA considers that there is a need for a stent dedicated to the treatment of intracranial arterial stenosis, and asked the expert advisors about the appropriateness of its assessment, to which all the expert advisors commented that there is no problem with such an assessment.

Based on the above comments of the expert advisors, PMDA concluded that despite the lack of data from a prospective study on the efficacy or safety of the Wingspan stent in the treatment of vascular dissection, acute occlusion, or impending occlusion, the procedural success rate in the Japanese clinical study, in which pre-deployment by a balloon was peformed as a general rule, was 73.7%, which is within the acceptable level as an emergency treatment. The appropriateness of the above conclusion of PMDA was discussed.

The following comments were raised from expert advisors:

- Since acute occlusion after PTA is a serious complication, there is a high need for a device for the treament of this complication, and the safety assessment of this use is appropriate.
- It is important that the Wingspan stent is available in Japan and, taking account of the results of the SAMMPRIS Trial, using the product to treat complications caused by PTA is reasonable.
- If the indication proposed by the applicant is not acceptable, the indication proposed by PMDA will have to be accepted instead.
- Post-PTA restenosis and elastic recoil should also be included in the indication because there is no other treatment option in case of recurrence.

PMDA decided to include "when there is no other effective treatment option" in the indication, taking account of the fact that although bypass surgery is available as a treatment for post-balloon PTA restenosis or elastic recoil, the surgery cannot be performed for certain sites. PMDA concluded that practice standards, guidelines, etc., should be established for the proper use of the Wingspan stent in cooperation with related academic societies.

The measures taken by PMDA were supported by the expert advisors.

IV. Results of Compliance Assessment by PMDA Concerning the Data Submitted in the New Medical Device Application and Conclusion by PMDA

[PMDA's conclusion on the results of GCP on-site inspection]

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application (H -1). As a result, it was found that in some medical institutions, the institutional review board reviewed the monitoring report submitted by the monitor based on the expedited review, and there were inconsistencies in descriptions between the source documents and the case report forms (missing description of adverse events). Thus, there were cases requiring improvements. However, since they were handled appropriately, PMDA has concluded that the clinical study as a whole was conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

[PMDA's conclusion on the results of document-based compliance assessment]
A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application. As a result, PMDA has concluded that there should be no problems with conducting a regulatory review based on the submitted product application documents.

V. Overall Evaluation

The Wingspan stent is a stent system consisting of a self-expanding nitinol revascularization device and a delivery system designed to maintain the lumen patency of the cerebral vessel through implantation at the stenotic site of an intracranial artery.

The major issues in the regulatory review of the Wingspan stent were as follows: (1) clinical evaluation and indication of the product and (2) proper use of the product. The conclusions of PMDA, taking account of discussions with the expert advisors, are as shown below.

(1) Clinical evaluation and indication of the product

The results of the Japanese clinical study were similar to those in the Wingspan and Gateway Safety Study, suggesting the possibility that the Wingspan stent may be a treatment option for patients who are refractory to medical therapy. However, PMDA has concluded that it should be taken into due account that the incidence of stroke in the target vascular region or death within 30 days after enrolment or procedure was higher in the group treated with the product in combination with aggressive medical management compared with the group receiving aggressive medical management alone in the SAMMPRIS Trial in the US which directly compared these groups, although the study subject population was different from that in the Japanese clinical study. The FDA modified the indication based on the results of the FDA's independent subpopulation analysis of the SAMMPRIS Trial data. However, PMDA has concluded that it is difficult to identify the target population in whom the benefit of the Wingspan stent outweighs the risk based on the results of the SAMMPRIS Trial for which no detailed data are available and on the submitted data from other studies, and that the modified US indication is not acceptable in Japan.

In Japan, intracranial arterial stenosis is treated with percutaneous transluminal angioplasty using a balloon angioplasty catheter. However, when angioplasty has caused vessel dissection, acute occlusion, or impending occlusion, or when the angioplasty has been found insufficiently effective, no approved medical device is indicated for such cases and a coronary stent is used off-label instead.

For the Wingspan stent to be effective in the treatment of vascular dissection, acute occlusion, or impending occlusion, it should be able to reach and be implanted at the lesion site. In the Japanese clinical study, the technical success rate (stenotic rate improved to <50% immediately after procedure) was 84.2%, and neither ipsilateral stroke nor death occurred within 6 months after the procedure in 2 patients who experienced vascular dissection during the procedure. Based on the above results, PMDA has concluded that it is clinically acceptable to use the product for treatment of vascular dissection, acute occlusion, or impending occlusion. Also, taking account of the fact that in the SAMMPRIS Trial, the incidence of "stroke in the target vascular region or death within 1 year" was 12.2% in the aggressive medical management group, whereas the rate was 20.0% in the PTAS-plus group, and that the indicence of "ipsilateral stroke or death within 6 months after the procedure" was 10.5% in the Japanese clinical study and 7.1% in the Wingspan and Gateway Safety Study, PMDA considers that the treatment using the Wingspan stent should not be conducted in preference to aggressive medical management. However, PMDA has also considers that there are no efficacy- or safety-related problems that contraindicate the use of the product in

the re-treatment after angioplasty in patients who do not respond to aggressive medical management and for whom no other effective treatment option is available.

Based on the above, PMDA has concluded that the indication of the Wingspan stent in Japan should be as follows:
The Wingspan stent is used in percutaneous transluminal angioplasty for intracranial arterial stenosis using a balloon angioplasty catheter in either of the following conditions:

- Emergency treatment of vascular dissection, acute occlusion, or impending occlusion caused during angioplasty
- Re-treatment of patients after angioplasty when there is no other effective treatment option

(2) Proper use of the product

PMDA has concluded that proper use of the Wingspan stent is essential in order to ensure the efficacy and safety of the product and for this purpose, guidelines, etc., should be established on the appropriateness of intracranial endovascular treatment of cerebral arterial stenosis in cooperation with related academic societies for the following reasons: (a) the SAMMPRIS Trial did not demonstrate the efficacy or safety of the product, and failed to show evidence that supports the use of the product in preference to aggressive medical management; (b) treatment with the Wingspan stent should not be performed if any other effective treatment is considered available, and PTA should be performed by taking into consideration the necessity of treatment with the product in a certain percentage of patients; (c) no restriction has been posed on the use of the balloon catheter for angioplasty which is approved for intracranial endovascular treament.

PMDA has also concluded that the following conditions for approval should be imposed: (i) appropriate measures should be taken to ensure that physicians with sufficient knowledge and experience use the Wingspan stent in compliance with the treatment guidelines established by related academic societies, and (ii) the product should be used in medical institutions with an established system for handling possible adverse events associated with intracranial endovascular treatment in order to prevent the aggravation of complications caused by percutaneous angioplasty of an intracranial artery.

On the basis of the above, PMDA has concluded that the Wingspan stent may be approved after modifiying the intended use with the approval conditions as shown below.

[Intended use]
The Wingspan stent is indicated for use in percutaneous transluminal angioplasty for intracranial arterial stenosis using a balloon angioplasty catheter in either of the following conditions:

- Emergency treatment of vascular dissection, acute occlusion, or impending occlusion caused during angioplasty
- Re-treatment of patients after angioplasty when there is no other effective treatment option

[Conditions for approval]
The applicant is required to:

1. Take appropriate measures in cooperation with related academic societies to ensure that the Wingspan stent will be used by physicians with sufficient knowledge and experience in the treatment of intracranial arterial stenosis at medical institutions with an established system for handling possible complications associated with the treatment.
2. Take appropriate measures in cooperation with related academic societies to ensure that that the Wingspan stent will be used, in compliance with the indication, by physicians (specified in 1 described above) who have acquired the skills of handling the product for endovascular treatment and sufficient knowledge of possible complications associated with the treatment by attending relevant training course or by other means.

3. Perform use-results surveys of all patients treated with the Wingspan stent until data from a specific number of patients have been accumulated, report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.

As the Wingspan stent is a new performance medical device, the re-examination period should be 3 years. The product is not classified as a biological product or a specified biological product.

The application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

VI. References

[1] Higashida RT, Meyers PM, Connors JJ, Sacks D, Strother CM, Barr JD, et al. Intracranial angioplasty & stenting for cerebral atherosclerosis: a position statement of the American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, and the American Society of Neuroradiology. *J Vasc Interv Radiol.* 2005 Oct;16(10):1281-5.

[2] Thijs VN, Albers GW. Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy.[see comment]. *Neurology.* 2000 Aug;55(4):490-7.

[3] Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation.* 2006 Jan;113(4):555-63.

[4] Kumai Y, Ibayashi S. Changes in the type of cerebral infarction over time and international comparison. *Japanese Stroke Databank.* 2005 ;46-47.

[5] Ecker RD, Levy EI, Sauvageau E, Hanel RA, Hopkins LN. Current concepts in the management of intracranial atherosclerotic disease. *Neurosurgery.* 2006 Nov;59(5)(SUPPLEMENT 3):S210-8.

[6] Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. *N Engl J Med.* 1985 Nov;313(19):1191-200.

[7] Hopkins LN, Budny JL, Castellani D. Extracranial-intracranial arterial bypass and basilar artery ligation in the treatment of giant basilar artery aneurysms. *Neurosurgery.* 1983 Aug;13(2):189-94.

[8] Hopkins LN, Budny JL. Complications of intracranial bypass for vertebrobasilar insufficiency. *J Neurosurg.* 1989 Feb;70(2):207-11.

[9] Marks MP, Wojak JC, Al-Ali F, Jayaraman M, Marcellus ML, Connors JJ, Do HM. Angioplasty for symptomatic intracranial stenosis: clinical outcome. *Stroke.* 2006 Apr;37(4):1016-20.

[10] Mazighi M, Yadav JS, Abou-Chebl A. Durability of endovascular therapy for symptomatic intracranial atherosclerosis. *Stroke.* 2008 Jun;39(6):1766-9.

[11] Kim JK, Ahn JY, Lee BH, Chung YS, Chung SS, Kim OJ, Kim WC, Joo JY. Elective stenting for symptomatic middle cerebral artery stenosis presenting as transient ischaemic deficits or stroke attacks: short term arteriographical and clinical outcome. *J Neurol Neurosurg Psychiatry.* 2004 Jun;75(6):847-51.

[12] Jiang WJ, Wang YJ, Du B, Wang SX, Wang GH, Jin M, Dai JP. Stenting of symptomatic M1 stenosis of middle cerebral artery: an initial experience of 40 patients. *Stroke.* 2004 Jun;35(6):1375-80.

[13] Bose A, Hartmann M, Henkes H, Liu HM, Teng MM, Szikora I, Berlis A, Reul J, Yu SC, Forsting M, Lui M, Lim W, Sit SP. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. *Stroke.* 2007;38:1531-1537.

[14] Zaidat OO, Klucznik R, Alexander MJ, et al. The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. *Neurology*. 2008;70:1518-1524

[15] Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, Hoh BL, Hourihane JM, Levy EI, Alexandrov AV, Harrigan MR, Chiu D, Klucznik RP, Clark JM, McDougall CG, Johnson MD, Pride GL Jr, Torbey MT, Zaidat OO, Rumboldt Z, Cloft HJ; SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* 2011;365:993-1003.

[16] Fiorella D, Levy EI, Turk AS, Albuquerque FC, Niemann DB, Aagaard- Kienitz B, Hanel RA, Woo H, Rasmussen PA, Hopkins LN, Masaryk TJ, McDougall CG. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. *Stroke*. 2007;38:881-887.

[17] FDA Executive Summary, Current Knowledge of the Safety and Effectiveness of the Wingspan Stent System with Gateway PTA Balloon Catheter for the Treatment of Intracranial Arterial Stenosis. (Prepared for the March 23, 2012 meeting of the Neurologic Devices Panel) http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM296664.pdf

[18] Connors JJ III, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. *J Neurosurg.* 1999;91:415– 423.

[19] Sakai N et al. Report of the study by Research Grant for Cardiovascular Diseases, 17C-1 from MHLW: Study on the preparation of the guidelines to ensure the safety of catheter intervention and to educate physicians in charge.